REMARKS

Claims 1-5, 8-31 and 34-37 are pending in the present application. By virtue of this response, no claims have been cancelled, amended, or added. Accordingly, claims 1-5, 8-31 and 34-37 are currently under consideration.

With respect to any arguments, claim amendments or cancellations, Applicants have not dedicated to the public or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Correction

In the amendment filed June 7, 2007, the undersigned agent stated:

> Claim 1 of Robinson lists over 100 categories of substituents that can be selected for each of the twelve substituents R1 through R12. Even assuming that each category contains only one choice, this results in over 12^{100} compounds represented in claim 1, or more than ... (10^{107}) compounds...

The statement above is incorrect; the correct figure is "only" over 100^{12} compounds, or 1,000,000,000,000,000,000,000,000, that is, over a trillion trillion compounds (10^{24}), which is 83 orders of magnitude less than the number of 10^{107} previously stated on June 7, 2007. The figure of 10^{107} was also used in the response of October 31, 2007, and should have been 10^{24} throughout that response as well. The undersigned agent regrets the error and any resulting confusion.

Information Disclosure Statement

An Information Disclosure Statement accompanies this response. The Applicants respectfully request consideration of the documents listed on the Form SB/08 by the Examiner.

The Examiner is respectfully requested to make the cited documents of record in the application and to return the initialed Form SB/08.

Claim Rejections – 35 USC § 112

Claims 21, 23-28 and 31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

These rejections are respectfully traversed. The rejection of claim 21 appears to have been inadvertently reiterated from the Office Action of January 11, 2007. The amendment filed on June 7, 2007 clarified that a mesoporphyrin formate (that is, a porphyrin without a central metal ion) is subjected to the metal insertion process, and the Examiner indicated in the Final Office Action mailed September 10, 2007 that the rejection had been overcome by amendment.

Regarding the rejection of claim 23 and its dependent claims 24-28 and 31, the Examiner also indicated in the Final Office Action that some of these same rejections had been overcome by amendment. The question "...where does the formate come from? There is no recitation of a step wherein the hemin is reacted with formic acid" appears to be a new rejection.

Regarding the formate anion, the second stage of the reaction of hemin with hydrogen in the presence of the hydrogenation catalyst can be done in formic acid; a formate salt of mesoporphyrin would result upon isolation of the mesoporphyrin. Alternatively, the mesoporphyrin can be placed in a formic acid solution and isolated. See, for example, paragraphs 0015-0017, pages 4-5 of the specification.

Finally, in the metal insertion process to obtain a metal mesoporphyrin halide, there is no metal initially present in the mesoporphyrin IX formate, and thus no need to replace any metal with tin. As indicated in Figure 3 and paragraphs 0014-0015 (page 4) of the instant specification, heating hemin with hydrogen and a hydrogenation catalyst (in Figure 3, palladium is used as the catalyst) results in removal of the iron ion of hemin, as well as reduction of the vinyl groups to ethyl groups, yielding un-metallated mesoporphyrin IX. Thus in this first step of the process, the iron is removed and is not replaced with any other metal.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph is respectfully requested.

Claim Rejections – 35 USC § U.S.C. 102

Claim 29 is rejected under 35 U.S.C. 102(b) as being anticipated by Goel *et al.* (WO 97/05152; document cited in IDS of 10/3/2006).

This rejection is respectfully traversed. Claim 29 recites that the metal mesoporphyrin formed by the method of claim 23 is a tin mesoporphyrin. Accordingly, Goel's cobalt-containing compounds do not disclose the limitations of the product-by-process claim 29. This rejection had been previously made in the Office Action of January 11, 2007, and addressed in the amendment filed on June 7, 2007. In the Final Office Action mailed September 10, 2007, the Examiner indicated that this rejection had been overcome by amendment, and it appears that this rejection is inadvertently reiterated. Withdrawal of this rejection is respectfully requested.

Claim Rejections – 35 USC § U.S.C. 103

Claims 2-5, 8-10, 22, 29-31 and 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Robinson (US Patent Pub. No. 2003/0100752) in combination with Drummond (Annals of New York Academy of Sciences, 1987, 514, 87-95) and Bettelheim *et al.* (General, Organic and Biochemistry, 1998, page 596), all of record.

This rejection is respectfully traversed. The Examiner states that "Robinson teaches tin mesoporphyrin complexed with amino acid (page 45, claim 1)..." (See page 5, second complete paragraph of the Office Action mailed December 12, 2007.) The Applicants respectfully submit that Robinson does not provide any guidance to select tin mesoporphyrin, with or without a complex with amino acids, out of the trillions of compounds embraced by claim 1. Selecting the substituents for the twelve R groups in Robinson's claim 1 in precisely the manner required to arrive at mesoporphyrins complexed with amino acids would require improper hindsight reasoning.

The Examiner states that "Drummond, drawn to metalloporphyrins, teaches control of heme metabolism using tin-protoporphyrins (page 87, introduction, last paragraph). Tin protoporphyrin was by far the most potent (page 88, Results and Discussion; page 89." (See page 5, last complete sentence and sentence bridging pages 5 and 6 of the Office Action mailed December 12, 2007.) However, Drummond does not mention tin or protoporphyrin on page 87. Drummond does state that "Sn-protoporphyrin was by far the most potent of the compounds examined" on page 88, but Sn-protoporphyrin has a K_I of 0.018 ± 0.001 μM, which is only about half that of Cr-protoporphyrin at 0.033 ± 0.009 μM (see Table 1 of Drummond, page 88). Note also that this statement is referring to *in vitro* activity, not *in vivo* activity. *In vivo* activity is unpredictable in view of *in vitro* activity; for example, Drummond indicates that cobalt protoporphyrin is an inhibitor *in vitro*, but induces the enzyme *in vivo* instead of inhibiting *in vivo* (see the last sentence of page 92, bridging onto page 93, and the subsequent sentences on page 93). Further, in Table 2 on page 89, the *in vivo* activity of chromium protoporphyrin was the most potent; Cr-protoporphyrin reduced rat liver heme oxygenase activity to 0.29 ± 0.04 nmol bilirubin/mg/hr. The next most potent compounds were manganese protoporphyrin and tin protoporphyrin, which reduced heme oxygenase activity to 1.05 ± 0.16 nmol bilirubin/mg/hr and 1.08 ± 0.13 nmol bilirubin/mg/hr, respectively (see Table 2 at page 89). Since these compounds are ultimately intended for use as pharmaceuticals, one would be guided to select the most active compound *in vivo*, not the most active compound *in vitro*. Assuming, for the sake of argument, that Robinson, Drummond, and Bettelheim could be properly combined, this would result in selection of chromium protoporphyrin-based compounds, not tin mesoporphyrin-based compounds.

The Examiner stated that "[p]roto- and mesoporphyrins are known in the art and are recognized as interchangeable because of their structural similarity." (Emphasis original) However, in the circumstances at hand, those two porphyrins are not interchangeable, and the results of *in vitro* experiments are not necessarily predictive of the results of *in vivo* experiments. For example, in the publication Drummond *et al.*, Arch. Biochem. Biophys. 255:64-74 (1987), accompanying this response, the researchers found that the *in vitro* inhibition (K_I) of tin protoporphyrin and tin mesoporphyrin are similar, at 0.011 μM and 0.014 μM, respectively. However, when administered to animals, tin mesoporphyrin was about ten-fold more effective in

lowering bilirubin production when compared to tin protoporphyrin. These unpredictable results indicate that protoporphyrin and mesoporphyrin are not interchangeable for the treatment of hyperbilirubinemia. The results of the Drummond Annals of the New York Academy of Sciences paper discussed in the previous paragraph also demonstrate this difficulty in predicting the relative activity of protoporphyrin and mesoporphyrin.

As the combination of Robinson, Drummond (Annals), and Bettelheim references does not provide the instantly claimed invention, and given the unpredictability of protoporphyrin activity versus mesoporphyrin activity, Applicants respectfully request withdrawal of this rejection.

Claims 11-28 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niedballa *et al.* (US 5,275,801).

Applicants respectfully traverse this rejection. As indicated previously, Niedballa's structure cannot encompass tin mesoporphyrin. The Examiner states that "[i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to make mesoporphyrins as instantly claimed by making insignificant changes to the method taught in the prior art." (See page 8, first sentence of the Office Action mailed December 12, 2007.) However, as noted above for the protoporphyrin and mesoporphyrin activity, changes to the porphyrin molecule can result in very different *in vitro* and *in vivo* activities. Thus, such allegedly "insignificant changes" can have very significant results. Furthermore, the Examiner has not provided a reason or motivation for making any changes to Neidballa, let alone specific changes resulting in mesoporphyrins, to arrive at the instant invention. Accordingly, the Applicants respectfully request withdrawal of this rejection.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing **docket no. 606952000500**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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